PEPSI-DOCK

A Detailed Data-Driven
Protein-Protein Interaction Potential
Accelerated By Polar Fourier Correlations

MACARON Workshop- March 21st 2017

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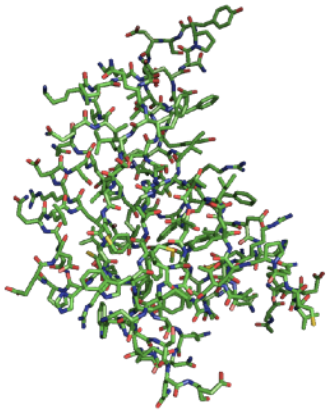
Nano-D & Capsid INRIA Teams

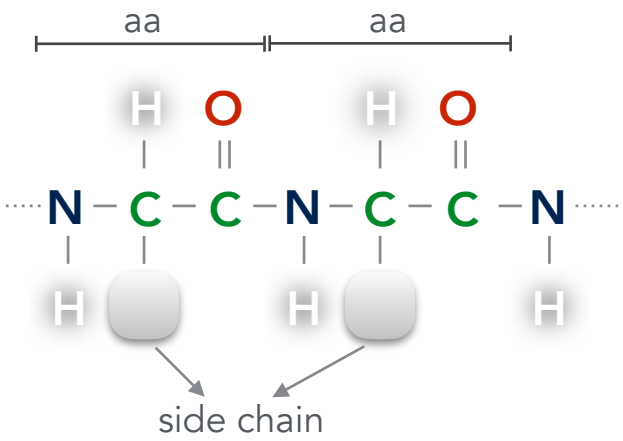
ABOUT PROTEINS

Definition

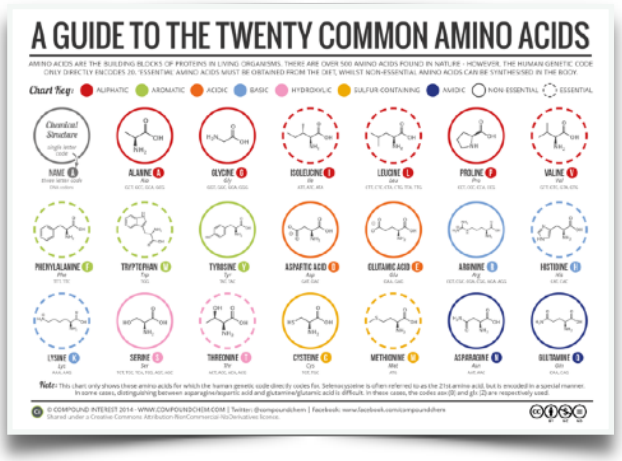
protein



(long) chain of amino acids (aa)



20 possible aa



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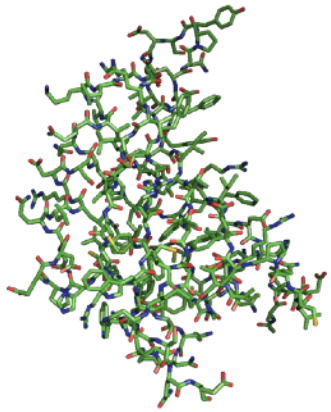

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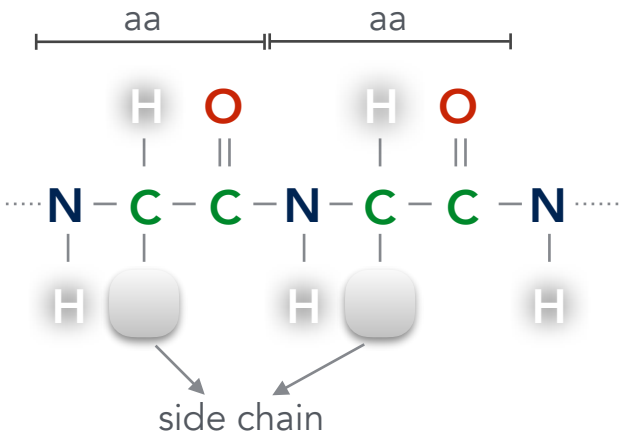

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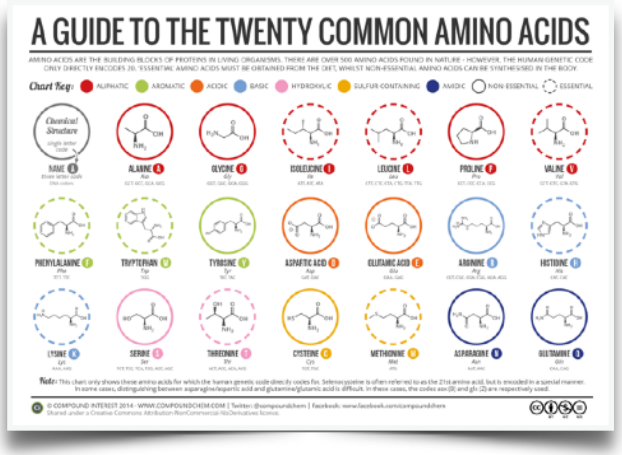
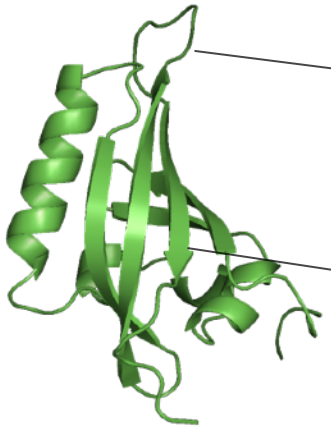


Representation

"cartoon"-like 3D structure



flexible pieces: structures not well-defined

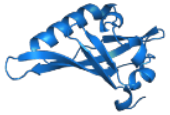
stable pieces: helices, parallel sheets

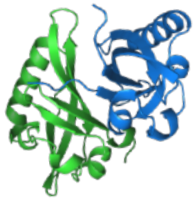
ABOUT DOCKING

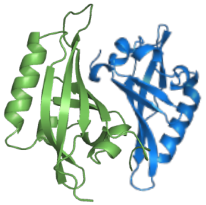
Structure Prediction

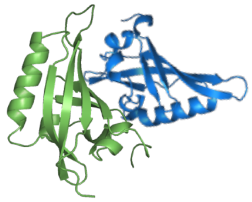
Protein - receptor

Protein - ligand



1. 

2. 

3. 

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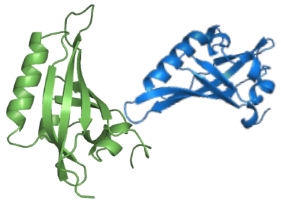
N. 

Whitehead, Timothy A., *et al*. Nature biotechnology 30.6 (2012)

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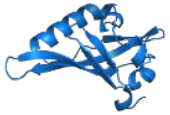

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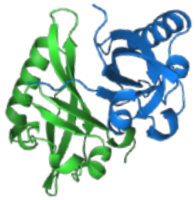

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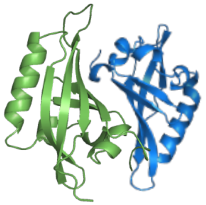

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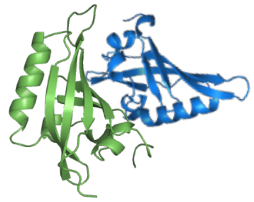

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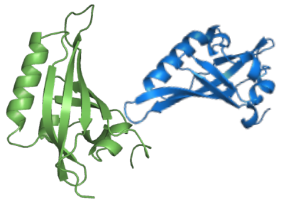
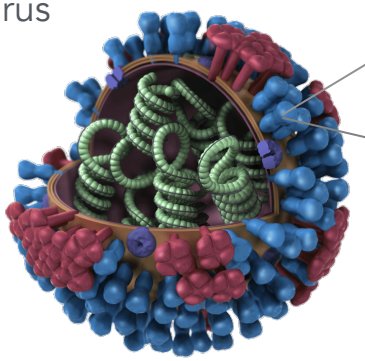
N.

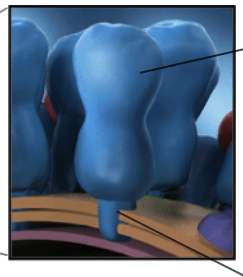


Why so important?

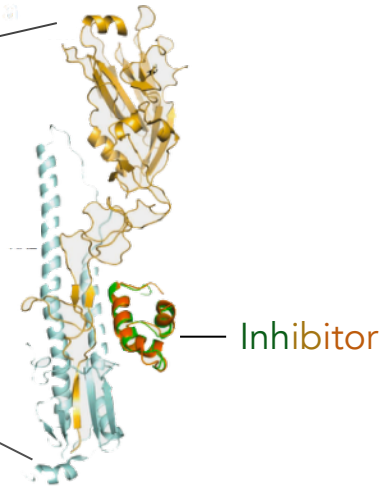
Influenza virus



100 nm



Hemagglutinin protein



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> 2001 Community-wide experiment: CAPRI (Critical Assessment of PRedicted Interactions)

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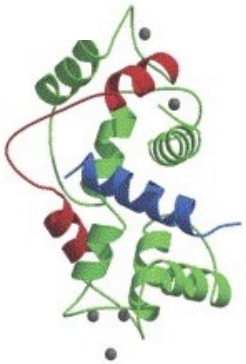
1. **Interaction energy** to score/assess the structures

Receptor

Ligand

Interaction energy



$$\Delta G_{\text{bind}} = \Delta H - T\Delta S$$

enthalpy

entropy

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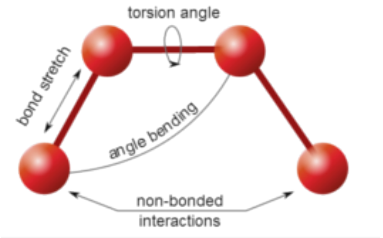
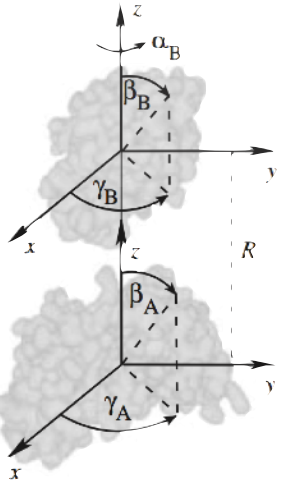


2. **Search algorithm** + set of parameters



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3. **Multilevel approach**: selection of top solutions ; restart with higher resolution

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starring

ZDock zdock.umassmed.edu

HexDock hex.loria.fr/hex.php

ClusPro cluspro.bu.edu

AutoDock autodock.scripps.edu

RosettaDock rosie.rosettacommons.org/ligand_docking

DOCK dock.compbio.ucsf.edu

and many others.....

PEPSI-DOCK

Polynomial Expansions of Protein Structures and Interactions for Docking

GOAL: To improve the first level : large and global search space

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Polynomial Expansions of Protein Structures and Interactions for Docking

GOAL: To improve the first level : large and global search space

Simple but accurate interaction energy approximation

- SVM-based algorithm to learn the atomistic potentials
- physically interpretable features:
  number densities of site-site pairs at a given distance
- arbitrarily shaped atomistic distance dependent interaction potentials

Popov, P., & Grudinin, S. (2015). J. Chem. Info. Model.
Knowledge of Native Protein–Protein Interfaces Is Sufficient To Construct Predictive Models for the Selection of Binding Candidates.

PEPSI-DOCK

Polynomial Expansions of Protein Structures and Interactions for Docking

GOAL: To improve the first level : large and global search space

Simple but accurate interaction energy approximation

Fast exploration

- rigid bodies assumption
- spherical Fourier correlation: complexity from $O(N^9)$ to $O(N^6 \log N)$

D.W. Ritchie, D. Kozakov, and S. Vajda, Hex code

PEPSI-DOCK

Polynomial Expansions of Protein Structures and Interactions for Docking

GOAL: To improve the first level : large and global search space

Simple but accurate interaction energy approximation

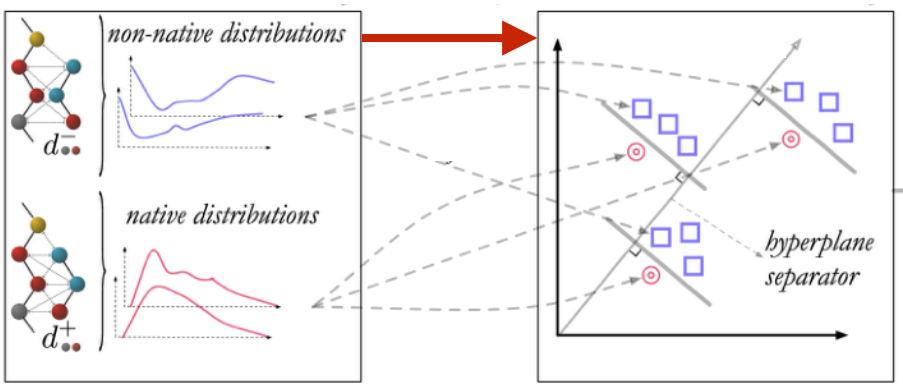
Fast exploration

Sparse representation in Gauss-Laguerre basis

1 Features extraction

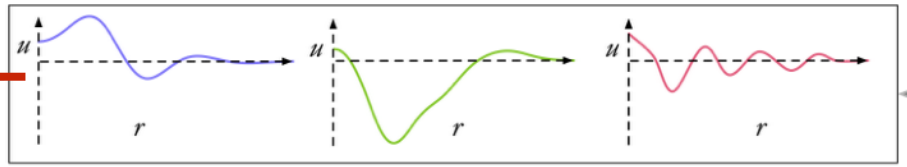
2 Sparse Representation

3
Optimisation



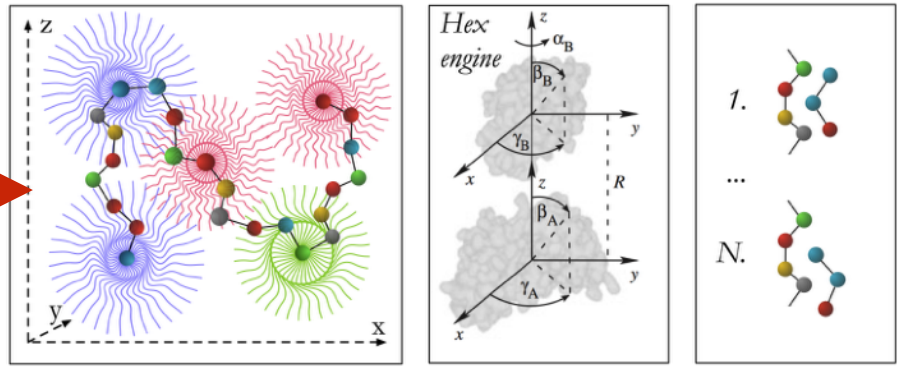
in
Gauss-Laguerre
basis

4 Stored 210 atomistic distance dependent potentials



5
From
1D to 3D

6 Fast exploration
of the search space

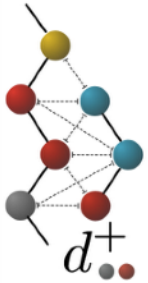


7
Ranked
docking
predictions

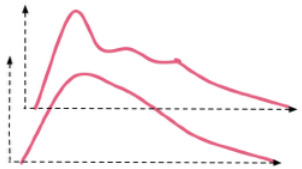
Detailed description of 1-D interactions at the interface

195 native non-redundant complexes

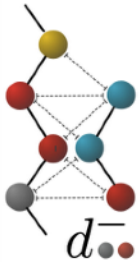
from ITScore Training Set
[Zou Lab, University of Missouri Columbia]



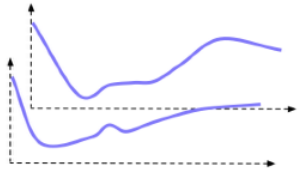
1-D native distributions of atom pairs /distance



40 000 generated false complexes



1-D non-native distributions of atom pairs / distance



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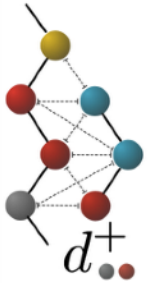

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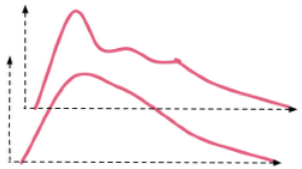
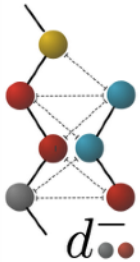
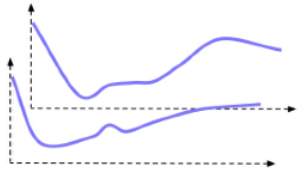


20 different atom types $\Rightarrow$ 210 interactions

40 000 generated false complexes



1-D non-native distributions of atom pairs / distance



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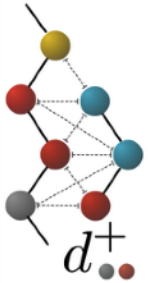

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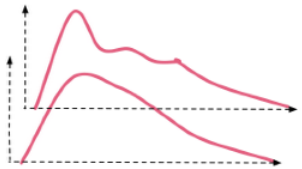

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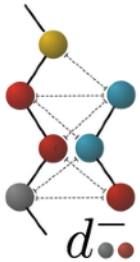

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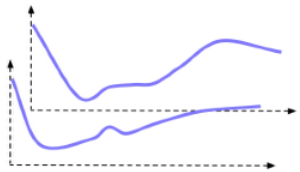
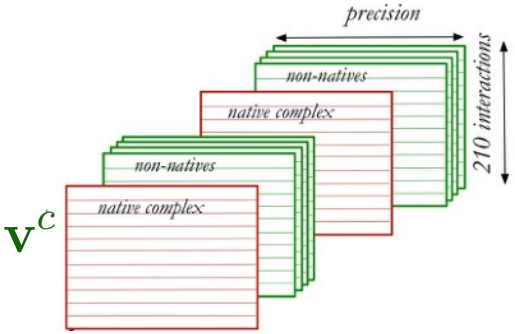


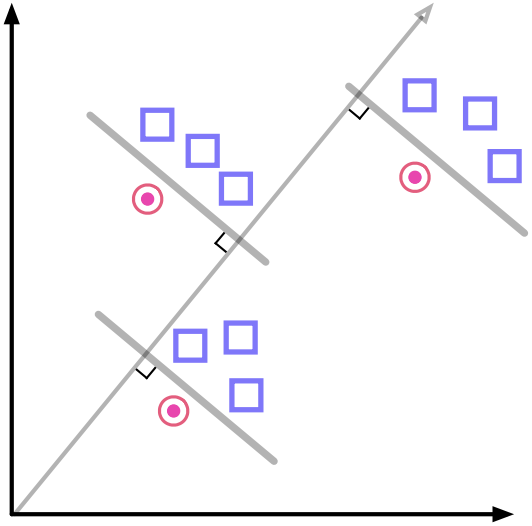
Sparse representation

in a Gauss-Laguerre polynomial basis
scaled to describe distributions up to 30 Å



about 6300 geometric features for each native and non-native complex

Optimal discrimination between native and non native interfaces



features $\mathbf{v}^c$; classifier **known**

- native complexes $y^c = 1$
- associated false complexes $y^c = -1$

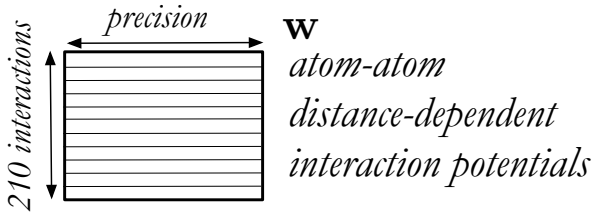
hyperplane separator **estimated**

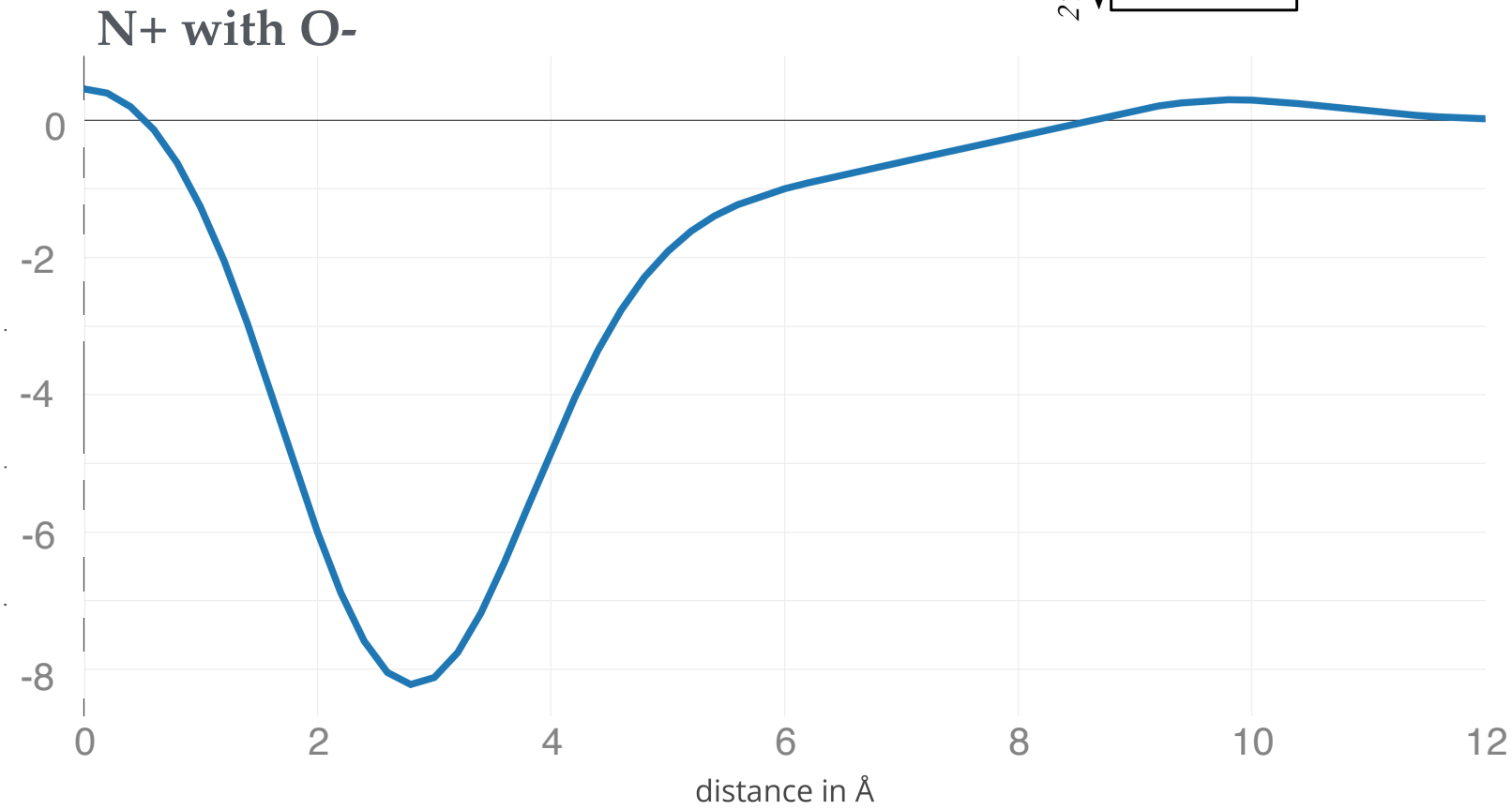
- $\mathbf{w}$ normal vector: 1-D interaction potentials
- $\mathbf{b}^c$ margin

Convex optimisation problem: Find **w** and $\mathbf{b}^c$ that minimise

$$\min_{\mathbf{w},\mathbf{b}^c} \underbrace{\frac{\lambda}{2}\|\mathbf{w}\|_2^2}_{\text{prevents overfitting}} + \underbrace{\gamma \sum_c \log\left(1 + e^{y^c(\mathbf{w}^T\mathbf{v}^c + \mathbf{b}^c)/\gamma}\right)}_{\text{penalises misclassification}}$$

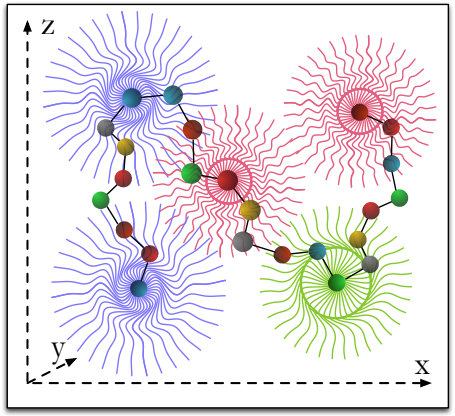
Knowledge of Native Protein–Protein Interfaces Is Sufficient
To Construct Predictive Models for the Selection of Binding Candidates.
Popov, Grudinin, 2015, *J Chem Info Model.*


precision
210 interactions
w
atom-atom
distance-dependent
interaction potentials


N+ with O-
0
-2
-4
-6
-8
0
2
4
6
8
10
12
distance in Å

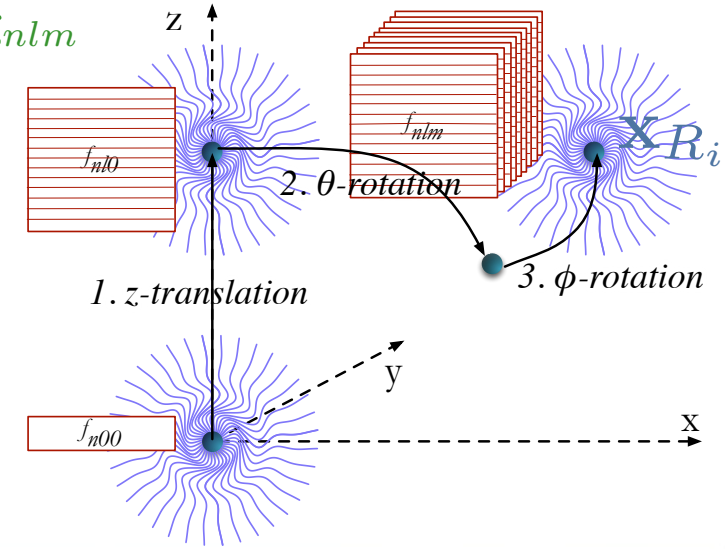
Linear sum of atom-atom convolution with potentials and densities

$$E = \sum_{\text{pairwise interactions } ij} \sum_{R_i} \sum_{L_j} \iiint_V f_{ij}(\mathbf{x} - \mathbf{x}_{R_i})\, g(\mathbf{x} - \mathbf{x}_{L_j})\, dV$$

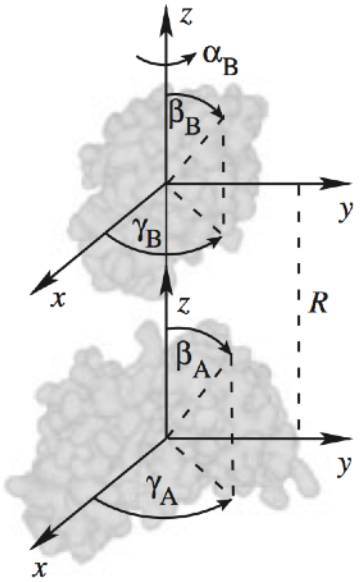


Representation with truncated polynomial expansion

$$\iiint_V f_{ij}(r) g(r - \mathbf{x}_{L_j}) dV = \sum_{nlm} \underbrace{(\mathbf{R}.\mathbf{T}.\mathbf{w})_{nlm}}_{=\mathbf{f}_{nlm}^{ij}} \cdot \mathbf{g}_{nlm}$$



Rigid body assumption



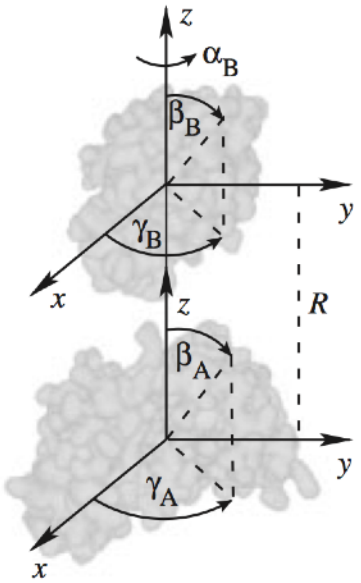
Energy depends to rigid positions of proteins

$$E(R, \beta_A, \gamma_A, \beta_B, \gamma_B, \alpha_B)$$

- 1 translation and 5 rotations to adjust
- discretised to enable exhaustive search

$$R \in [0 : 1 : 40\ \mathring{A}]$$
$$\alpha \in [0 : 7.5 : 360^o]$$
$$(\beta, \gamma) \in [0 : 7.5 : 180^o]^2$$

Rigid body assumption



Energy depends to rigid positions of proteins

$$E(R, \beta_A, \gamma_A, \beta_B, \gamma_B, \alpha_B)$$

- 1 translation and 5 rotations to adjust
- discretised to enable exhaustive search

$$R \in [0 : 1 : 40\ \mathring{A}]$$
$$\alpha \in [0 : 7.5 : 360^o]$$
$$(\beta, \gamma) \in [0 : 7.5 : 180^o]^2$$

Fast exhaustive search

Truncated expressions using spherical Fourier correlation

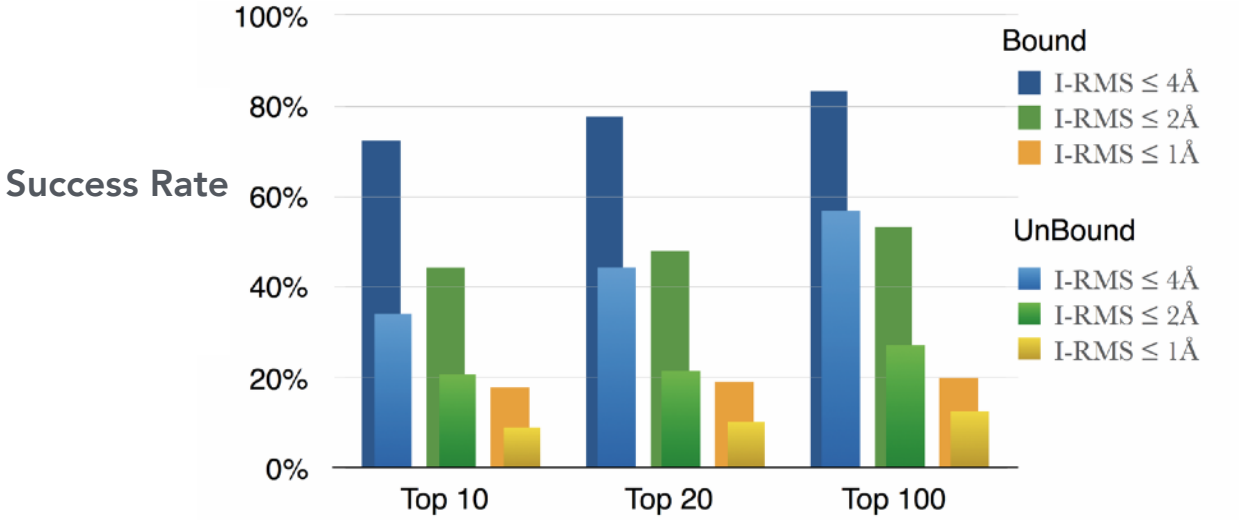
$$E(R, \beta_A, \gamma_A, \beta_B, \gamma_B, \alpha_B) = \mathrm{DFT}^{-1}\left[\mathrm{DFT}\left(\mathbf{R}_{\beta_A,\gamma_A}\mathbf{T}_R\mathbf{f}_A\right).\mathrm{DFT}\left(\mathbf{R}_{\alpha_B,\beta_B,\gamma_B}\mathbf{g}_B\right)\right]$$

complexity from $O(N^9)$ to $O(N^6 \log N)$: **10^9 poses in ~ 10 min**

Accelerating and Focusing Protein-Protein Docking Correlations Using Multi-Dimensional Rotational FFT Generating Functions. D.W. Ritchie, D. Kozakov, and S. Vajda (2008). *Bioinformatics. 24 1865-1873.*

Test on 88 complexes from the Docking Benchmark Set v5.0 for which the separation distance ≤ 30 Å

Docking Benchmark Set = the only existing benchmark to compare different docking algorithms
[Hwang, Vreven, Janin, Weng, 2010]



Comparison on v4.0

Top 10 for I-RMS ≤ 2.5Å

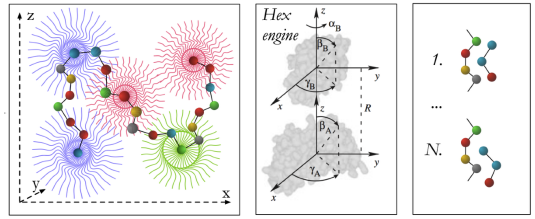
Category (Nb. of Complexes)	ZDOCK.	SwarmDock	PEPSI-Dock
Easy (45)	12	11	13
Medium (15)	1	1	1
Difficult (15)	0	0	0

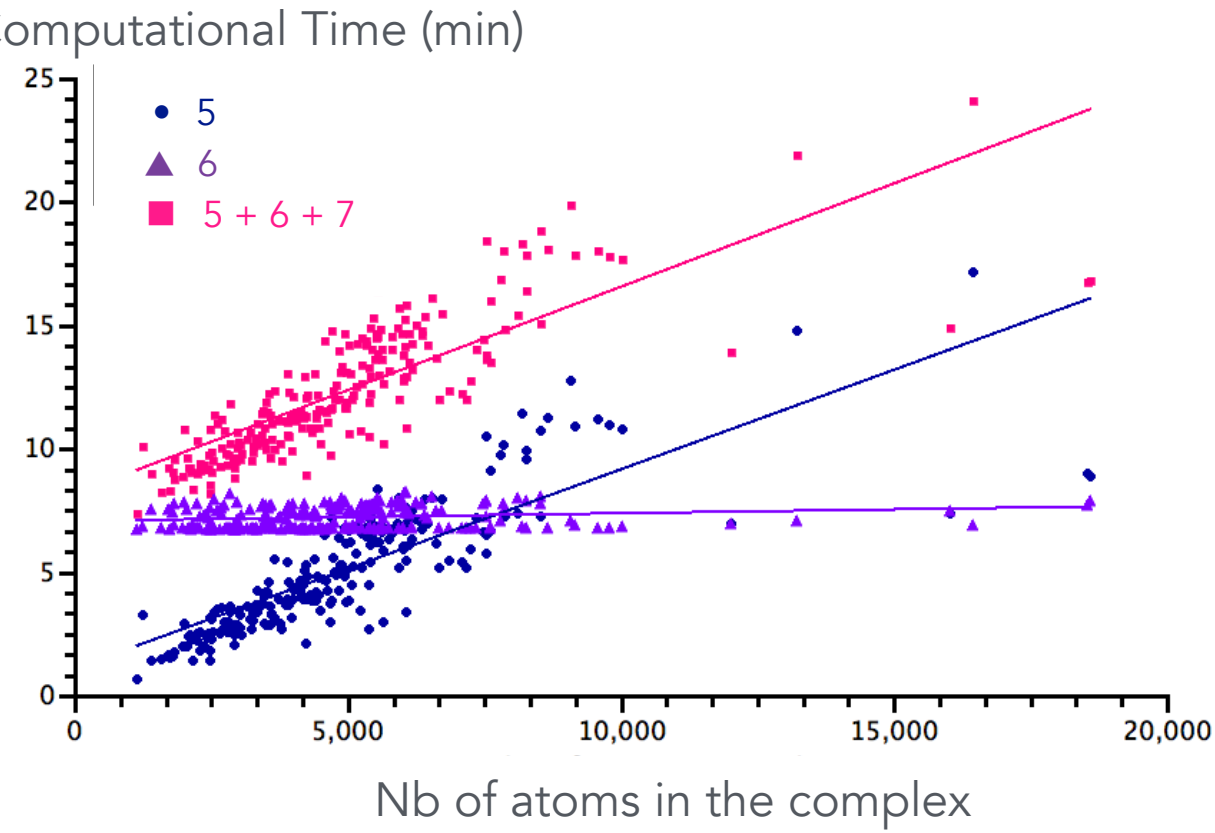
Running Time of PEPSI-Dock measured on a modern laptop

5 preprocessing

6 docking

7 sorted list





Docking of 10^9 poses in less than 10 min on a laptop ~ weeks of a 1 µs MD simulation

PEPSI-DOCK

Polynomial Expansions of Protein Structures and Interactions for Docking

A docking automatic algorithm for the first stage of the docking pipeline

- novelty: arbitrarily -shaped + distance-dependent potentials combined with a FFT search sampling technic

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1. Improve unbound predictions: use other training set

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- **Large distances** ⚠️ **loss of precision**
- **Unbound sets: similar results than SwarmDock or ZDOCK**
- **Adaptation to other types of interactions** 

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TO DO

1. Improve unbound predictions: use other training set
2. Deal with the docking of large proteins: use other sampling

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PEPSI-Dock, Neveu *et al.*, Bioinformatics, 2016

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ANR

https://www.samson-connect.net

ANY QUESTION?